Haemostasis in malignant disease

M. J. AUGER, MB, MRCP, *Research Fellow*
*University Department of Haematology, Royal Liverpool Hospital, Liverpool**

M. J. MACKIE, MD, MRCP, MRCPath, *Consultant Haematologist*
Department of Clinical and Laboratory Haematology, Western General Hospital, Edinburgh

Since the original description of thromboembolic disease occurring in association with cancer [1], a great deal of evidence has accumulated to suggest important interactions between cancer cells and the haemostatic system. Such interactions may manifest themselves in a clinical setting in the form of vascular thrombosis and haemorrhage or appear subclinically as isolated abnormalities of laboratory tests. Furthermore, there is now evidence that fibrin deposition around tumours may promote tumour growth and that pharmacologic modulation of the haemostatic system may impair growth and spread of tumour cells.

Following a brief synopsis of normal haemostasis, the clinical and laboratory abnormalities of haemostasis encountered in patients with malignant disease will be reviewed, followed by discussions of the pathogenesis, significance and treatment of these abnormalities.

Normal haemostasis

The clot-forming or coagulation system is balanced by the clot-dissolving or fibrinolytic system. The key step in the blood coagulation system is the conversion of fibrinogen to fibrin by thrombin with the formation of a small peptide, fibrinopeptide A (FPA) as a byproduct, and the subsequent crosslinking of fibrin polymers to form a stable clot. The thrombin required in this reaction may be formed by either the intrinsic clotting system, so called because it results from the interaction of plasma proteins (ie clotting factors) present in the circulating blood, or via the extrinsic clotting system requiring tissue factor, which is extrinsic to circulating blood (Fig. 1.) and is found in extracts of various tissues.

Plasmin, formed by the activation of plasminogen, is the key enzyme of the fibrinolytic system. Its natural substrate is fibrin and the degradation products of fibrin (FDPs) can be measured in the circulation (Fig. 1).

Platelets play an important role in normal haemostasis at several steps. They provide the phospholipid surface on which the coagulation reactions proceed, adhering and aggregating at sites of endothelial damage, and they contribute some coagulation factors.

*Address for correspondence: Dr. M. J. Auger, University Dept of Haematology, Royal Liverpool Hospital, Prescot St, PO Box 147, Liverpool L69 3BX

Clinical abnormalities of haemostasis in patients with malignant disease

Thrombosis and bleeding are well recognised complications of malignancy and provide the most dramatic evidence for interactions between cancer cells and the haemostatic system. Generally, thrombotic episodes are commoner in patients with solid tumours, and bleeding more common in those with leukaemia, though they may coexist. For example, both haemorrhagic symptoms and vascular occlusive episodes are frequent complications of myeloproliferative disorders such as polycythaemia rubra vera, and both may occur in the same patient. The incidence of vascular occlusive episodes in these patients seems to be related to the haematocrit [2] and the bleeding diathesis to abnormalities of platelet function [3].

Thrombosis

The association of thromboembolic disorders with malignant disease was first recognised over one hundred years ago, when Armand Trousseau reported a high incidence of venous thrombosis in patients with gastric carcinoma [1]. Later, clinical and post-mortem studies described arterial and venous thrombosis, pulmonary embolism, thrombophlebitis migrans and nonbacterial thrombotic endocarditis in association with a variety of malignant tumours [4,5].

The incidence of clinical thromboembolic phenomena in patients with malignant disease has been reported to vary between 1 and 11 per cent [6–8], though the incidence in specific tumour types is difficult to ascertain as it may change in time as a function of many variables, including tumour prevalence, chemotherapy and improved noninvasive techniques used for the diagnosis of thromboembolic disease (TED). The incidence in post-mortem studies of cancer patients is much higher than in clinical studies [9,10].

Historically, pancreatic carcinoma has been associated with the greatest risk of TED [4,10], though the total number of cases of TED is now higher in patients with carcinoma of the lung because of the greater prevalence of that tumour [11]. Prostatic carcinoma has not been associated with a significantly increased risk of TED [12], but such patients appear to be at greater risk when treated

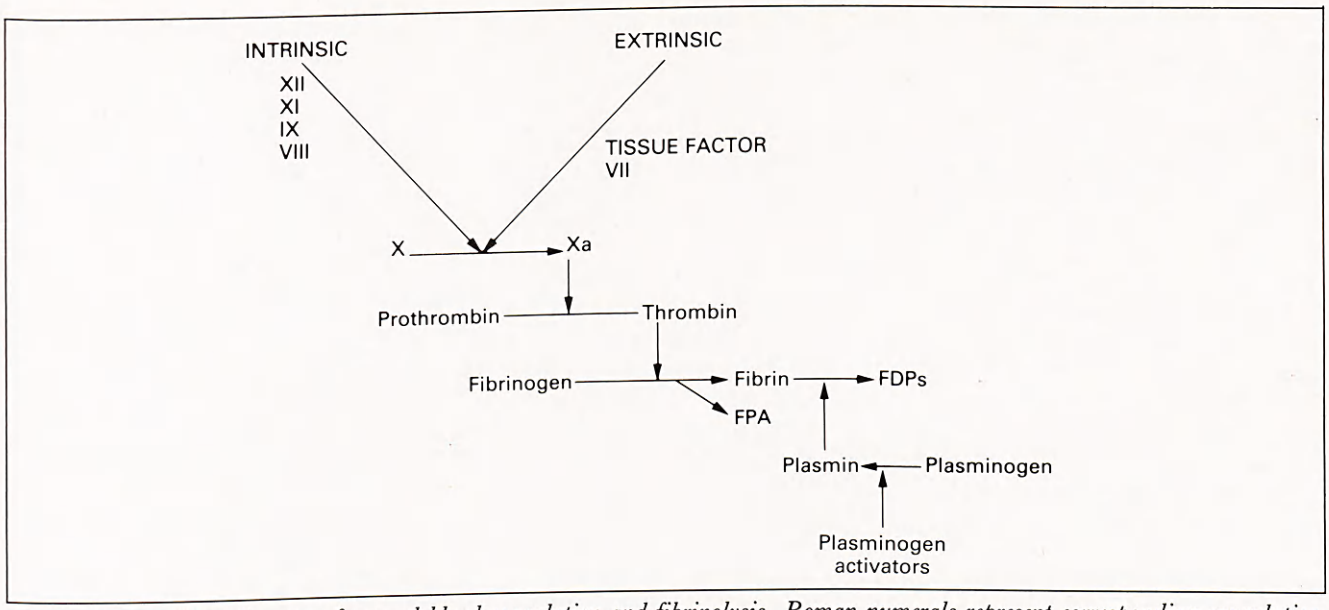

Fig. 1. *A simplified diagram of normal blood coagulation and fibrinolysis. Roman numerals represent corresponding coagulation factors, FDPs—fibrin degradation products; FPA—fibrinopeptide A.*

with either oestrogens or chemotherapy [13]. Patients with breast cancer treated with chemotherapy were found to have a higher incidence of thrombotic phenomena while receiving chemotherapy than when this was discontinued [14]. Surgical procedures likewise increase the risk of TED in patients with cancer to a greater extent than in patients with nonmalignant conditions. Thus, Pineo reported that 10 of 30 patients with cancer developed deep venous thrombosis following abdominothoracic surgery [15], as opposed to 14 of 134 subjects undergoing similar procedures for nonmalignant disease ($p < 0.005$).

TED may precede clinical evidence of malignant disease by months or even years. Thrombophlebitis migrans, characterised by thrombosis in unusual sites which are both migratory and resistant to anticoagulation, is accepted as a clue to the presence of occult malignancy and may occur years beforehand. Gore and colleagues [16] demonstrated that the far commoner form of venous thrombosis, deep venous thrombosis and its complication pulmonary embolism, should alert clinicians to occult cancer. They retrospectively ascertained the incidence of cancer before and after pulmonary embolism was diagnosed by pulmonary angiography in 128 patients. The incidence of cancer before pulmonary embolism (12%) was essentially the same as that in a comparison group of patients without pulmonary embolism (10%). In the two years after pulmonary angiography however, cancer was diagnosed in 13 (14.7%) of 88 patients with pulmonary embolism in contrast to none of 82 patients in the comparison group [16]. Conversely, a much smaller follow-up study of 17 patients with unexplained deep venous thrombosis failed to show an increased risk of cancer [17].

On the basis of such studies, one cannot recommend an exhaustive search for occult cancer in all patients with venous thromboembolism. However, the possibility of an occult malignancy should be considered during the clinical assessment of any patient with TED. Careful follow-up is also required both because of the risk of recurrent venous thromboembolism and to remain vigilant for signs or symptoms of malignancy.

Bleeding

Bleeding episodes may occur in patients with solid tumours, but they are more common in patients with acute leukaemia and especially acute promyelocytic leukaemia where the incidence of haemorrhage may approach 90 per cent. The bleeding may be clinically mild and present with easy and spontaneous bruising, purpura, ecchymosis, gastrointestinal and genitourinary haemorrhage or bruising at sites of invasive procedures. Conversely, the bleeding may be a life threatening intracranial or intraperitoneal haemorrhage. Haemorrhage is the most common haemostatic complication encountered in acute leukaemia. It precedes other symptoms in 50 per cent of patients and it remains an important cause of death [18].

Bleeding is less common in patients with solid tumours. In a large series of patients with a variety of malignancies [19] only six of 108 patients had bleeding episodes. They were menorrhagia associated with acute leukaemia in one patient, gastrointestinal bleeding from carcinoma of the colon in two patients and from carcinoma of the stomach in a further two patients and bleeding from cancer of the oral cavity in one patient. In another study [5], nine of 77 patients had spontaneous bleeding requiring transfusion, but in all of these patients the platelet count was less than $39{,}000 \times 10^6/l$ with a normal fibrinogen concentration. The authors concluded that clinically significant bleeding in patients with solid tumours was primarily a manifestation of thrombocytopenia.

Excessive bleeding in malignancy may be caused by

various means including thrombocytopenia, decreased synthesis of coagulation factor proteins due to hepatic metastases, or intravascular coagulation. A study of patients with acute leukaemia showed that significant haemorrhage often occurred in the presence of normal 'routine' coagulation studies. However, combinations of increased thrombin, plasmin and nonspecific protease activities correlate well with major clinical bleeding episodes [20]

Laboratory abnormalities of haemostasis in patients with malignant disease

Blood coagulation

There have been many reports detailing changes of haemostatic factors in subjects with malignant disease [19,21,22]. The most frequent alterations are elevated levels of clotting factors (particularly fibrinogen, factors V and VIII) and fibrin degradation products (FDPs), accompanied by changes in platelet numbers ranging from thrombocytopenia to thrombocytosis. A state of low grade intravascular coagulation with secondary fibrinolysis is thought to cause these alterations, the high levels of clotting factors being usually explained by an increased synthesis overcompensating an accelerated consumption [11]. Despite the abundance of reports, many provide limited information as they have often been carried out on unselected series of patients with a range of tumour types at different stages of progression, who had undergone different therapy. As a result, it is difficult accurately to determine the incidence of abnormalities of routine coagulation tests in patients with cancer, though Sun reported at least one abnormal test in 106 of 108 patients with cancer and five or more abnormal tests of coagulation in 74 (68%) of these patients [19]. Other studies, however, have been unable to demonstrate any consistent abnormalities of routine coagulation tests in subjects with cancer [23,24].

Less simple but more sensitive tests of *in vivo* coagulation such as a radioimmunoassay for fibrinopeptide A show that low-grade coagulation activation occurring with tumours is an early phenomenon, eventually occurs in virtually all cases of malignant disease and may be used to estimate the spread and activity of the malignant process [25,26]. However, if such sensitive techniques are employed, it is of great importance to exclude nonmalignant causes of an elevated fibrinopeptide A level, such as infection or thromboembolic disease, before concluding that disease progression has occurred.

Fibrinolysis

Abnormalities of fibrinolysis in patients with malignancy have been less commonly demonstrated. The reported incidence of elevated levels of FDPs varies from 9 to 68 per cent in different studies [8,19]. Recent studies show the plasma level of plasminogen activator and its inhibitor to be increased in patients with pancreatic and colorectal carcinomas with and without metastases [27]. This suggests that, unlike the situation with blood coagulation,

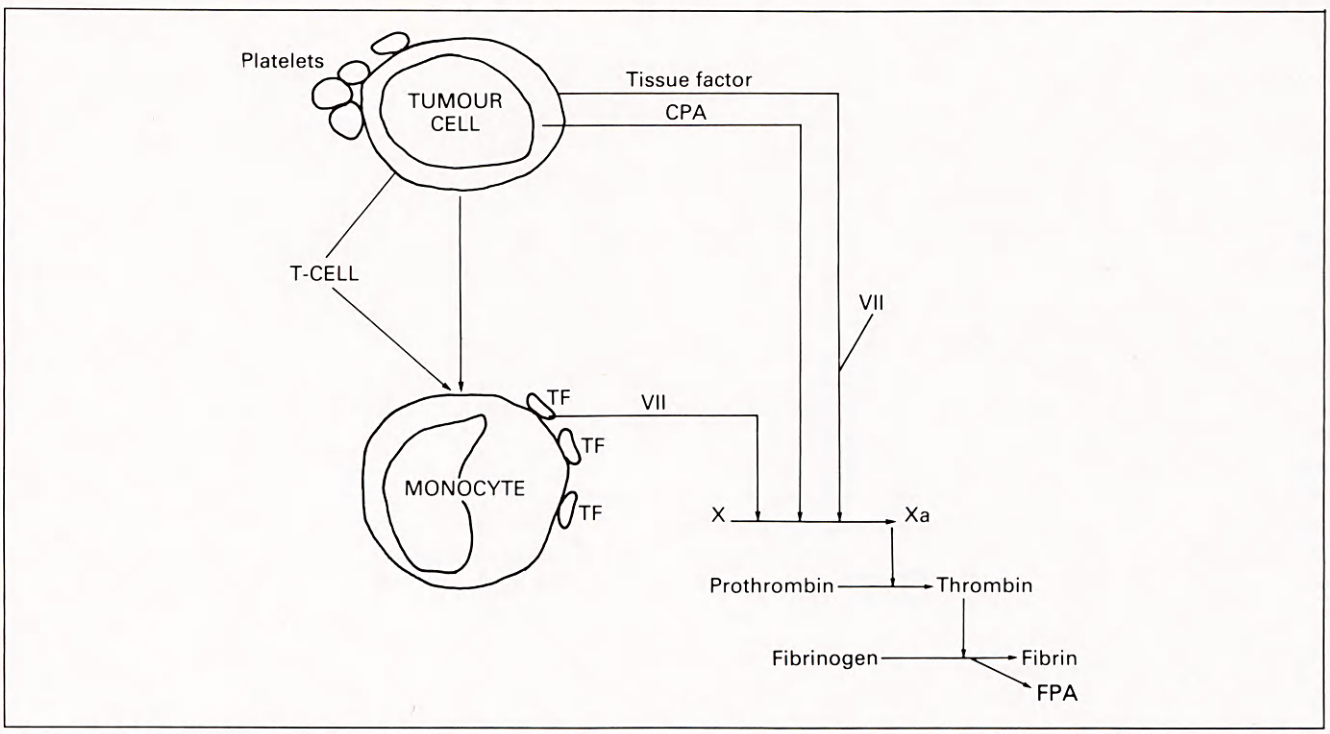

Fig. 2. *Diagramatic representation of interactions between tumour cells, monocytes and the haemostatic system. (TF—tissue factor; CPA—cancer procoagulant A; FPA—fibrinopeptide A.)*

malignant transformation *per se* may result in increased production and secretion of plasminogen activator and its inhibitors, rather than it being a correlation with the extent of such a process. Granulocytes can produce an elastase-like protease that digests coagulation factors and increased activity has been recorded in acute myeloid leukaemia in association with bleeding and raised levels of fibrin degradation products [28].

Pathogenesis of haemostatic abnormalities in malignant disease

Procoagulant (clot promoting) and fibrinolytic (clot lysing) activity was described in extracts of human and experimental tumours 30 years ago [29,30]. Since then, further evidence has accumulated indicating possible interactions of cancer cells with the haemostatic system. Concepts of the pathogenesis of such interactions include the production of procoagulants and plasminogen activators by tumour cells themselves, the production of procoagulants by activated mononuclear phagocytes (monocytes and macrophages) and the activation of platelets by tumour cells (Fig. 2).

Cancer cell procoagulants

Studies of different tumours and cell lines have established that tumour cells may produce at least two types of procoagulant activity: tissue factor (tissue thromboplastin) and cancer procoagulant A, which acts as a proteolytic enzyme capable of directly activating factor X [31].

Tissue factor, a potent activator of the extrinsic clotting system, has been reported in a number of tumours of animal and human origin, including cases of human small cell lung carcinoma and leukaemic cells from patients with acute promyelocytic leukaemia.

Cancer procoagulant A (CPA) was detected in the partially purified mucus of mucin-secreting adenocarcinomas and was found directly to activate factor X to Xa. This procoagulant has also been isolated from primary melanomas and may be responsible for the low-grade intravascular coagulation observed in melanoma patients, particularly in those with metastatic lesions.

Other procoagulants of uncertain specificity have been described in cell cultures and tissue extracts, but difficulties of purification and lack of species specificity in assays makes interpretation difficult.

Monocyte/macrophage procoagulants

It has become clear in recent years that peripheral blood monocytes and their tissue counterparts, macrophages, are not only important in the immune response to a foreign antigen but are also capable of activating blood coagulation in response to a variety of stimuli including endotoxin, immune complexes and complement components. The procoagulant which has been most consistently found in human monocyte preparations is tissue factor [32] which is expressed on the cell surface. There is now evidence to show that peripheral blood monocytes from human subjects with breast and lung cancers express increased amounts of tissue factor when compared to monocytes from normal subjects and that a strong positive correlation exists between monocyte procoagulant activity and *in vivo* blood coagulation [33,34]. Whether this monocyte 'activation' occurs as a result of tumour-specific antigens activating T lymphocytes, immune complexes or other mechanisms is not established.

Tumour cell–platelet interactions

Ultrastructural studies have shown tumour emboli in the lungs surrounded by platelet aggregates, suggesting an important role for platelets in tumour spread. Also, certain tumour cells aggregate platelets *in vitro* and this has been correlated with metastatic potential. Activation and aggregation of platelets may go some way to explaining the thrombocytopenia seen in some cases of malignant disease. Platelet aggregating material has been extracted from some tumour cell lines, and other evidence suggests one or more cell surface glycoproteins can aggregate platelets directly.

These studies have led to the concept that platelets may have a role in the sequestration, adherence and penetration of tumour cells through the blood vessel endothelial cell barrier, preventing their rapid clearance from the circulation and allowing extravascular formation of 'nests' of tumour cells [35].

Cancer cell plasminogen activators

Some tumour cells produce enzymes that can activate plasminogen and thereby activate fibrinolysis. Malignant transformation of breast tissue is associated with the significantly increased production of plasminogen activators by the cancer cells [36]. So called plasminogen activators may be the most widely distributed mechanism used by tumour cells for generating localised extracellular proteolysis [37]. This may have a more important role in local invasion by tumour cells than intravascular fibrinolysis.

Significance of haemostatic abnormalities in malignant disease

Two lines of evidence suggest abnormal haemostasis may play an important role in the pathogenesis of tumour growth and spread: histologic and pharmacologic.

Histologic evidence

In 1878 Billroth reported his autopsy observations [38] that human tumour cells were found frequently in association with thrombi and postulated that metastases occur when a portion of the tumour-thrombus complex breaks off and forms a tumour embolus. More recent work using immunochemical and ultrastructural studies has confirmed the presence of fibrin deposition in and around both animal and human tumours. Studies of small cell lung cancer, breast cancer and renal cell carcinoma have shown that fibrin is deposited in association with viable tumour cells in these particular tumour types [39].

Pharmacologic evidence

Well controlled human studies of anticoagulant drugs in cancer are limited. The Veterans Administration Cooperative Study on the use of warfarin [40] in the treatment of small cell lung cancer in 50 patients showed that the median survival of patients who received warfarin in addition to standard chemotherapy (50 weeks) was significantly greater than the median survival of subjects who received chemotherapy alone (26 weeks, $p = 0.026$). The median length of time to evidence of tumour progression was also increased significantly in the warfarin group ($p = 0.03$). However, other studies have been less optimistic and the results of larger studies are awaited with interest.

The role of antifibrinolytic drugs such as tranexamic acid, or antiplatelet drugs in patients with malignancy is unclear. The few studies have generally been on small numbers of patients and often not well controlled. Animal studies have been more numerous but their relevance to human systems is uncertain. Generally, animal tumour models suggest that coumarin anticoagulants reduce metastasis formation, antifibrinolytic drugs reduce metastases from transplanted tumour cells though not from intravenously administered tumour cells and some, though not all, tumours respond to platelet function inhibitors [41]. Clearly, these agents may have different effects in different tumour models at different stages of tumour growth and results should be interpreted with caution.

Treatment of haemostatic abnormalities complicating malignancy

A characteristic of thromboembolic disease complicating malignancy is that it is often refractory to conventional anticoagulant treatment [7]. Two such cases, recently described, illustrate the difficulties encountered in these subjects [42]. Both heparin and warfarin treatment were tried, but only heparin seemed effectively to control the thrombosis.

The paucity of well controlled clinical trial data precludes a rational approach to treatment in many of these patients. However, a patient with severe recurrent thrombotic episodes should receive intravenous heparin. This would then usually be replaced by oral coumarin anticoagulants, though there remains some doubt as to the efficacy of coumarin anticoagulants in patients with malignant disease [4,42]. In those patients who have recurrent TED on warfarin therapy, adjusted subcutaneous heparin could be administered every 12 hours. The dose is set by adjusting the dose given over the first three days of therapy to maintain the mid-interval-activated partial thromboplastin time (determined six hours after injection) at 1.5 times the control value [43]. Though this regime has not been assessed in patients with malignant disease, it has been shown to be effective after an uncomplicated deep venous thrombosis [43], in contrast to conventional, fixed, low-dose heparin (5000 U given subcutaneously every 12 hours) which is associated with a 47 per cent incidence of recurrent venous thromboembolism [44]. A similar regimen may be beneficial for the prevention of TED in patients with malignancy undergoing surgery, where conventional low-dose heparin therapy is inadequate.

Bleeding associated with disseminated intravascular coagulation but without clinical evidence of thrombosis is treated by replacement of coagulation factors and platelets. Heparin has not been shown to be of clear benefit in these patients, though an exception appears to be acute promyelocytic leukaemia where it is of possible benefit [45], athough vigorous replacement with platelets and coagulation factors is essential.

Currently, low-grade intravascular coagulation complicating malignancy is not treated with anticoagulants when unaccompanied by thrombotic or haemorrhagic manifestations. Clinical trials have demonstrated that warfarin can reduce the fibrinopeptide A level in cancer patients [24], but heparin has had variable effects, reducing the fibrinopeptide A level in some patients without demonstrable intravascular thrombosis [46] and in others reducing it only if there is a concomitant intravascular thrombosis [24,25].

Conclusions

Patients with malignant tumours are at risk of developing thromboembolic disease before or after the tumour is clinically apparent. If sensitive tests of *in vivo* blood coagulation are used, most patients with cancer have low grade intravascular coagulation. Although some progress has been made in defining the underlying mechanisms, there is still uncertainty surrounding the precise mechanism by which fibrinogen is converted to fibrin, though tumour cell and monocyte products appear to be important. The precise significance of coagulation and fibrinolytic abnormalities is unclear, but histologic and pharmacologic evidence suggests an important role for the haemostatic system in tumour growth and spread. The thromboembolic disease is often refractory to conventional anticoagulant treatment and a greater understanding of the pathogenesis of the haemostatic abnormalities is required before a rational approach to treatment can be applied.

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